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Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression

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ABSTRACT

Opioid treatment of pain is generally safe with 0.5% or less events from respiratory depression. However, fatalities are regularly reported. The only treatment currently available to reverse opioid respiratory depression is by naloxone infusion. The efficacy of naloxone depends on its own pharmacological characteristics and on those (including receptor kinetics) of the opioid that needs reversal. Short elimination of naloxone and biophase equilibration half-lives and rapid receptor kinetics complicates reversal of high-affinity opioids. An opioid with high receptor affinity will require greater naloxone concentrations and/or a continuous infusion before reversal sets in compared with an opioid with lower receptor affinity. The clinical approach to severe opioid-induced respiratory depression is to titrate naloxone to effect and continue treatment by continuous infusion until chances for renarcotization have diminished. New approaches to prevent opioid respiratory depression without affecting analgesia have led to the experimental application of serotinine agonists, ampakines, and the antibiotic minocycline.

OPIOID analgesics remain the most commonly used drugs in the treatment of moderate to severe postoperative pain. The opioids that have been used for decades (such as morphine, methadone, and fentanyl) have become accepted treatments and are administered to patients by anesthesiologists under standard protocols. Side effects related to opioid use have become well known and may be managed appropriately, with nausea, vomiting, sedation, and respiratory depression being associated commonly with postoperative analgesic doses. However, these side effects should not be trivialized. Postoperative nausea and vomiting is common and distressing to patients, and excessive sedation may contribute to increased morbidity and mortality.[1,2] However, it is perhaps respiratory depression that remains the main hazard of opioid use, uppermost in the minds of nurses and physicians, because of the obvious risk of fatal outcome. The first recorded human fatality from a morphine overdose dates from the 1850s.[3] The Englishman Alexander Wood (1817–1884) performed one of the first injections of morphine to his wife who subsequently died from respiratory depression. The toxic effects of morphine were noted earlier by Sertürner,[4] the German pharmacist who was the first to isolate morphine from opium in 1806. In 1817, he published his discovery together with reports of the administration of the alkaloid to himself, three young boys, three dogs, and a mouse. One of the dogs died while he described the effect that morphine had on himself and his three young "volunteers" as near fatal.[4,5]

Since the recognition in the 1960s that opioid ligands exert their biologic effects *in vivo* through interactions with multiple opioid receptors, namely μ-, δ-, and κ-opioid receptors,[6] it has been recognized that opioid-induced respiratory depression is mediated largely by the μ-opioid receptor(s). This has been substantiated more recently using the technique of knockout mice lacking selective receptor gene products. In knockout mice lacking μ-opioid receptors, in contrast to mice with active μ-opioid receptors, administration of morphine and other opioids failed to induce respiratory depression (or centrally mediated antinociception).[7,8] These findings confirm that μ-opioid receptors are the key targets for opioid-induced respiratory depression. Further, the observation that respiratory depression and antinociception seem to act *in tan-*

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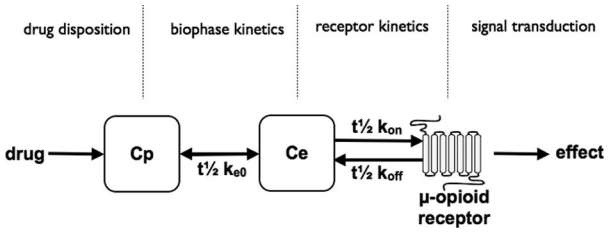

Fig. 1. Pharmacokinetics and pharmacodynamics of an opioid. After injection of a drug into the blood stream, it spreads across the various tissues (drug disposition). From the plasma (with concentration Cp), it crosses the blood-brain barrier to reach the effect compartment ($t½k_{e0}$ = the blood effect-site equilibration half-life) with concentration Ce. At the opioid-receptor site, the drug interacts with the receptor (receptor kinetics) with a constant for receptor association (k_{on}) and dissociation (k_{off}), here depicted as half-lives $t½k_{on}$ and $t½k_{off}$. For naloxone, $t½k_{e0}$ = 6.5 min and $t½k_{off}$ = 0.82 min; for buprenorphine, $t½k_{e0}$ = 75 min and $t½k_{off}$ = 70 min; and for fentanyl, $t½k_{e0}$ = 5–15 min and $t½k_{off}$ < 0.1 min.

dem supports the concept that stimulation of μ-opioid receptors may result invariably in both actions.

Today, we are aware that to minimize the risk of moderate-to-severe respiratory depression, it is essential that we fully understand the pharmacokinetics and pharmacodynamics of analgesic opioids (fig. 1) and establish clear, reliable drug treatments to reverse (*i.e.*, treat) opioid-induced respiratory depression. Fortunately, perhaps, the commonly used opioid-receptor antagonist naloxone provides a good standard safety cover for reversal of opioid-induced respiratory depression.[9] However, with the intensity and duration of the respiratory depressant effects dependent on the pharmacological characteristics and dose of the administered opioid, it is also important that the pharmacodynamics and pharmacokinetics of any antagonist, including naloxone is also well characterized to achieve adequate reversal and appropriate for any situation.[10,11] It is the intention of the current review, therefore, to consider the important relationships between the commonly used analgesic opioids and the ability of drugs, particularly of naloxone, to reverse opioid-induced respiratory depression. Because opioid analgesia and respiratory depression arise from the identical gene product, naloxone use will invariably cause reduction or possibly even loss of analgesic efficacy. Therefore, we will also review developments in the possible use of alternative drugs for the purpose of reversing and/or effectively preventing opioid-induced respiratory depression without compromising analgesia.

We will address the following items: (I) incidence of opioid-induced respiratory depression in patients treated with opioids for acute (postoperative) pain, (II) naloxone reversal of opioid-induced respiratory depression, (III) naloxone side effects, and (IV) nonopioid reversal/prevention of opioid respiratory depression.

Incidence of Opioid-induced Respiratory Depression in Postoperative Patients

In most, if not all studies, the respiratory effects of opioids are quantified by the observed changes in breathing frequency and/or oxygen saturation (Spo_2). For example, in a series of studies in the 1990s, Wheatley and coworkers[12–15] used Spo_2 as a measure of respiratory effect and defined postoperative hypoxemia as Spo_2 < 94% with moderate hypoxemia as Spo_2 < 90% and severe hypoxemia as Spo_2< 85% for more than 6 min per hour. Definitions of what levels may constitute respiratory depression, however, will vary between practices or studies (*e.g.*, Catley *et al.*[16] who used Spo_2 level of < 80%). With respect to breathing frequency, severe respiratory depression is considered at breathing rates of less than 8–10 breaths/min. It is important to understand that oxygen saturation and breathing frequency are surrogate indicators of ventilatory drive and provide only limited information on the effects of a drug on the ventilatory control system (*e.g.,* oxygen saturation is a measure of gas exchange in the lung rather than a direct indicator of ventilatory efficacy).[17] Inspired minute ventilation and arterial carbon dioxide concentration in clinical settings and the hypercapnic ventilatory response in experimental settings are direct measures of ventilation and ventilatory drive but are often difficult to assess on a continuous basis. However, Spo_2 is a simple measurement used commonly to indicate a serious opioid-induced ventilatory event, perhaps together with even looser indicators of respiratory depression such as sedation and bradypoea (*i.e.*, low breathing frequency).

There have been various studies comparing different routes of administration of opiates, particularly morphine, on respiratory depression in postoperative care. In a meta-analysis of intramuscular, epidural, and intravenous analgesia (including patient-controlled analgesia [PCA]), the incidence of opioid-induced respiratory depression as defined by low-breathing frequency was less than 1%.[18] Most of the studies included were designed to compare analgesic effects, but respiratory effects, if any, were usually reported as side effects. Data from a large meta-analysis including 15 clinical trials (comparing intramuscular morphine (10 mg) in 486 patients with placebo in 460 patients) indicate that the occurrence of minor adverse effects were more common with morphine (34%) than with placebo (23%), but major adverse events were rare and did not differ between morphine and placebo (morphine 0.6% and placebo 2%).[19] Absence, or very low incidence, of respiratory depression with single or repeated doses of intramuscular morphine (10 mg) is a common finding of postoperative studies, exemplified by a very recent study in which a 10-mg dose of morphine was compared on intramuscular and intravenous administration to 38 patients with postoperative pain after hip replacement surgery.[20] Neither treatment caused severe respiratory depression. Epidural and intrathecal administration of opioids was shown in the 1980s and 1990s to provide effective and long-lasting postoperative analgesia, and the use of low-dose opioids was advocated.[21,22] In two large reviews of more than 14,000 and 11,000 patients receiving opioids extradurally, with the majority being administered morphine for the treatment of postoperative, traumatic, and cancer pain, the incidence of severe respiratory depression was 0.09% and 0.2%, respec-

tively.[23,24] In 1,100 patients receiving opioids intrathecally, 0.36% demonstrated delayed ventilatory depression.[23]

However, perhaps the most important use of opioids postoperatively is through intravenous self-administration with PCA devices, and a greater number of safety studies with larger patient numbers have been reported with this approach.[25] PCA morphine, usually of around 1 mg bolus doses with a 5–10 min lockout period and administered for widespread uses, is concluded to be generally associated with a low incidence of respiratory depression, typically between 0.2 and 0.5%.[26–31] This may be illustrated in more detail by referring to a review of a database of approximately 1,600 PCA patients in Canada.[30] Eight patients (approximately 0.5%) demonstrated severe respiratory events on receiving PCA morphine. These observed rates of respiratory depression with the general use of PCA morphine, however, may be somewhat higher in more selective groups of postoperative patients. Citing a report by Wheatley *et al.*,[27] in the United Kingdom, of 510 patients recovering from major surgery who received 1 mg/ml of morphine in boluses of 1 mg with a lockout time of 5 min, 10 patients were recorded with a breathing rate of less than 10 breaths/min (2%) and 4 required the use of intravenous naloxone (0.8%). In New Zealand, in an analysis of 300 patients receiving PCA morphine for acute postoperative pain (from a total patient number of 5,759), 6 patients (2%) were reported with severe respiratory depression of less than 8 breaths/min, 5 of which had received a bolus dose of morphine of 2 or 2.5 mg.[31] The incidence of respiratory depression after the use of morphine PCA is often reported as associated with the use of higher doses of opiate when trying to achieve pain relief (or overdose error in PCA use).[31,32] In agreement with this, there are also several studies demonstrating a higher incidence of patient respiratory depression if a background infusion of morphine is used in conjunction with PCA.[28,29] Although all the reported incidences of severe respiratory depression cited were successfully managed by the administration of naloxone, the potential for morbidity and even mortality still exists.[31] Overall, therefore, overt opioid-induced postoperative respiratory depression requiring intervention by the anesthesiologist or acute pain service may be concluded to be rare whatever the route of administration, although the risk seems greater with higher opioid doses. However, the risk of opioid-induced respiratory depression must always be taken into account. In his review of 8 PCA cases of respiratory depression, Etches[30] discusses that the true incidence of respiratory compromise associated with postoperative opioid analgesia, whatever the route of administration, may be higher than that reported for two reasons, first that retrospective data, which is often the source of published reports, may not always record the reasons for interventions, and second, that respiratory depression may be reported as sedation or bradypnoea and episodes of nonsymptomatic severe hypoxemia (without sedation or bradypnea) may go unreported. A higher incidence of respiratory depression is observed in clinical trials where morphine has been used as a standard, comparator drug and where, because the patient is being monitored very closely at many time points postoperatively, a higher incidence of single, noncritical episodes of severe respiratory depression may be observed. For example, in a randomized, double-blinded comparison of morphine and morphine-6-glucuronide administered subcutaneously by PCA after orthopedic surgery, 14 of 48 (29%) patients receiving PCA morphine (2-mg bolus doses with a lockout of 10 min) had respiratory rates that decreased below 8 breaths/min at one or more time points during the 24 h after baseline.[33]

It is important to mention here that although opioid-induced respiratory depression is uncommon in the typical perioperative patient (American Society of Anesthesiologists classification I–III), there are various patient groups who are at higher risk, including the morbidly obese, patients who suffer from sleep apnea, patients with specific neuromuscular diseases, the very young (premature babies, children with breathing problems during sleep), the very old, and the very ill (American Society of Anesthesiologists Classification IV–V). Proper identification of these patients and adequate postoperative monitoring are a prerequisite to reduce analgesia-related respiratory events.

Naloxone Reversal of Opioid-induced Respiratory Depression

Reversal of Full Opioid Agonists (Morphine, Fentanyl, and Congeners)

Two opioid antagonists are available clinically as rescue medications for serious opioid-induced side effects: naloxone and naltrexone. Naloxone is United States Food and Drug Administration approved for therapeutic use in the reversal of opioid-induced activity and adverse reactions postoperatively, including respiratory depression. Naltrexone is approved for use in alcoholism and opioid dependence.[34] Clinically, naloxone has been shown in many studies to reverse effectively and rapidly respiratory depression induced by opioid full agonists, such as morphine and fentanyl.[34–37]

Naloxone is an allyl-derivative of noroxymorphone and first synthesized in 1960 (fig. 2). It is a nonselective competitive opioid antagonist at the μ-, δ-, and κ-opioid receptors.[38] Naloxone inhibits all pharmacological effects of opioids and, in line with classic receptor theory, produces a parallel right shift in the dose-response curves of opioids.[39] Naloxone is readily absorbed after oral administration, but its low bioavailability makes naloxone less suitable for this administration route. After oral administration, naloxone is metabolized extensively in the liver (first-pass effect $>$ 95%). It is primarily metabolized into the inactive conjugate naloxone-3-glucuronide. After intravenous infusion, approximately 70% is excreted through the kidney as conjugated naloxone metabolites and 30% as unchanged naloxone.[40]

The extent and duration of naloxone-induced reversal of opioid-induced respiratory effects is highly variable and related to many factors, including the specific opioid used, the opioid dose, administration mode, concurrent medication,

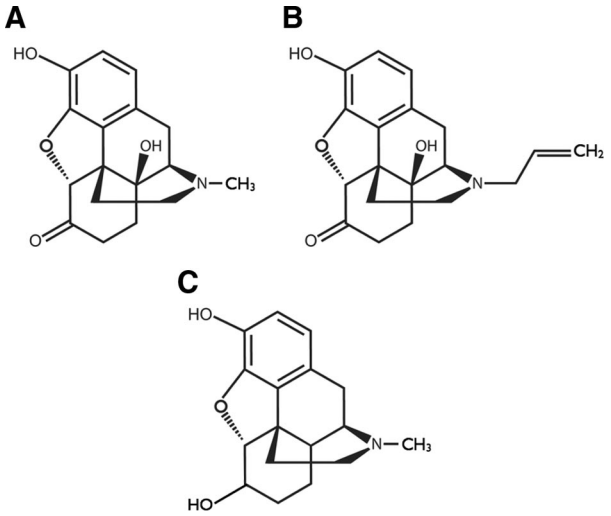

Fig. 2. Chemical structures of (*A*) oxymorphone, (*B*) naloxone, and (*C*) morphine.

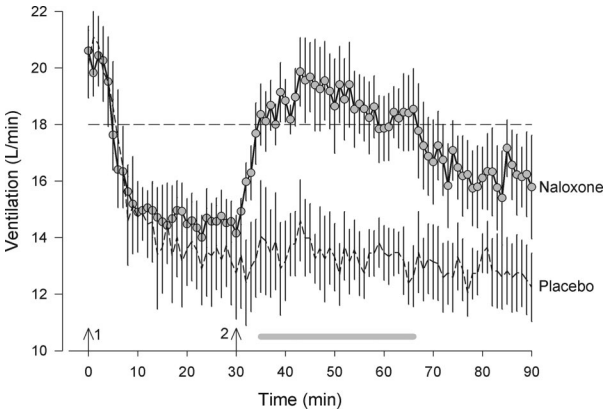

Fig. 3. Reversal of morphine-induced respiratory depression by naloxone. Data are the mean (±SEM) of 16 subjects. Subjects breathed a hypercapnic gas mixture (end-tidal P_{CO_2} clamped at 55 Torr) causing their baseline ventilation to be about 20 l/min. At *Arrow* 1, 0.15 mg/kg intravenous morphine is administered. At *Arrow* 2, either 0.4 mg naloxone iv or placebo is given as bolus infusion. In the naloxone group, ventilation increased rapidly toward baseline. The *dashed line* represents baseline ventilation − 10% × baseline ventilation (= 18 l/min). Naloxone caused ventilation to exceed this value for 30 min (represented by gray bar). Unpublished observation (Albert Dahan, M.D. Ph.D., September 2009).

underlying disease, pain and the state of arousal, genetic make-up of the patient, and exogenous stimulatory factors.[41] It is, therefore, important to understand the pharmacokinetics and pharmacodynamics of the specific opioid agonist, antagonist, and their interactions for effective and safe reversal of opioid-induced respiratory depression.

For naloxone, the relationship between dose of agonist and antagonist for respiratory depression has been demonstrated quantitatively in mice. Apparent pA_2 values (log of the affinity constant K_B) were determined for the antagonism by naloxone of the respiratory depressant effects of three opioid agonists: morphine, levorphanol, and pentazocine; the apparent pA_2 values were not significantly different for the three opioids (apparent pA_2 = 7.35, 7.49, and 7.46, respectively), indicating that all three drugs most probably interact with the same receptor (*i.e.*, the μ-opioid receptor) to induce respiratory depression.[42] To obtain these pA_2 values, as a competitive antagonist at the μ-opioid-receptor complex, the activity dose response curves to opioid agonists are shifted in parallel to the right in the presence of naloxone. Hence, the higher the dose of opioid agonist administered, the greater the dose of naloxone needed to reverse the opioid effects (particularly of the respiratory depressant effects observed with the higher agonist doses). The receptor association or dissociation kinetics (fig. 1) for naloxone are fast. *In vitro*, the half-life of dissociation ($t_{½}k_{off}$) of the naloxone-opioid human μ-opioid-receptor complex has been estimated at 0.82 min, and *in vivo* it may be assumed to be fast also.[43] After systemic administration, naloxone gains ready access to and even distribution throughout the brain. In mice, after subcutaneous administration of [^{3}H]naloxone, the naloxone concentration in the whole brain was related to the dose administered (and unaffected by the simultaneous administration of morphine) and evenly distributed across the four brain areas examined (pons-medulla, cerebellum, midbrain, and cerebral cortex).[42] Access to the brain by naloxone, and hence the μ-opioid-receptor, is rapid[40,44]; the blood effect-site equilibration half-life is short ($t_{½}k_{e0}$ = 6.5 min), indicating rapid transfer and equilibrium of naloxone from the plasma to the site of action in the brain.[45] Incidentally, but important when constructing pharmacokinetic or pharmacodynamic models, the plasma effect-site transfer half-lives ($t_{½}k_{e0}$) for fentanyl and its analogs are also short (5–15 min, depending on the measured endpoint), whereas morphine is much longer (2–3 h).[46] *In vivo*, therefore, the concentration of naloxone at the central μ-opioid receptors may be assumed to be proportional to the injected dose, the dissociation rate at the receptor complex to be fast, and consequently, receptor kinetics not to be rate limiting in the observed biologic actions of naloxone. More important to the biologic half-life of naloxone, therefore, is its pharmacokinetics in plasma. After intravenous infusion of naloxone to healthy volunteers, the estimated elimination half-life of naloxone from plasma was 33 min.[45] In a recent study in 16 healthy volunteers without pain, the respiratory changes induced by the intravenous administration of morphine (0.15 mg/kg) were reversed completely by introduction of a standard dose of naloxone (0.4 mg).[47] However, reversal of morphine was short lived with a rapid return to full respiratory depression (renarcotization after 30 min), as shown in figure 3.

All opioid agonists with a longer plasma half-life than naloxone have a hypothetical potential to show renarcotization with time, especially when bolus doses of naloxone are used. This is commonly not seen in clinical practice because opioid concentrations are often just above the threshold for respiratory depression, and treatment with a single or just a few effective bolus doses of naloxone is sufficient to reverse the respiratory depression induced by most opioids for the short time that the agonist concentration exceeds the respiratory depression threshold (an exception is buprenorphine,

see the next section Reversal of the Partial Opioid Receptor Agonist Buprenorphine). Often cumulative naloxone titration doses much less than 400 μg are then sufficient. Note that respiratory depression occurs at higher receptor occupancy than some degree of analgesia, and hence, analgesia is not compromised when titrating naloxone to (respiratory) effect. However, this evidently does not apply to the setting of drug abuse or suicide attempt. It also does not apply to shorter acting opioids, such as alfentanil, when continuous zero-order infusion regimes are applied. Such an approach may have benefits in minimizing the fluctuations in drug plasma levels, but agonist infusions have obvious implications for the time scale for the reversal by naloxone. In two studies in healthy volunteers, the respiratory depressant effects of a continuous infusion of alfentanil were reversed rapidly and completely by a single bolus infusion of naloxone (approximately 0.4 mg).[47,48] However, if the alfentanil infusion is maintained, the depressant effects of alfentanil were reasserted within the hour.[48] Possibly, improved infusion regimens such as by using target-controlled infusion may reduce the chance of respiratory depression without compromising analgesia.

One strategy that has been investigated to prevent the recurring return of opioid adverse events is the use of continuous or repetitive naloxone infusion. In small-scale studies, fixed-dose infusions of naloxone of approximately 4–8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ were used to maintain postoperative patients breathing effectively after having received morphine, sufentanil, or fentanyl.[49] This strategy has been expanded more recently to investigate whether infusions of naloxone could be titrated in an up-and-down manner to maintain adequate spontaneous respiration after high-dose fentanyl anesthesia.[50] Patients ($n = 59$) scheduled for elective surgery for visceral cancer received an infusion of fentanyl (40 μg/kg for more than 30 min before incision followed by a basal infusion of 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and, after surgery, extubation was assisted and maintained by the administration of naloxone. Naloxone boluses were administered as required to achieve set extubation criteria, followed by an up-and-down program of naloxone infusions to maintain adequate analgesia combined with adequate breathing. The mean total doses of naloxone were for extubation 3.4 ± 2.6 μg/kg and for maintenance 26.9 ± 23.2 (mean ± SD) μg/kg over a mean 10.8 ± 6.7 h (mean 2.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$). In the postoperative period, manipulating the naloxone infusion rates as required successfully resolved any symptoms observed. It should be noted perhaps that one patient was excluded from the postoperative part of the study because of failure to establish adequate spontaneous respiration with the maximal dose of naloxone for extubation (600 μg).

A different strategy has been advocated for remifentanil, a μ-opioid agonist with a similar analgesic potency to fentanyl, but a very fast onset ($t_{½}k_{e0} = 1$ min) and an ultra-short duration of action caused by rapid hydrolysis to an inactive metabolite (plasma elimination $t_{½} = 3$ min).[46,51] In healthy volunteers, remifentanil-induced respiratory depression and its reversal by naloxone have been investigated. Twelve subjects received remifentanil as low-dose (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or high-dose (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusions, and all subjects showed significant reductions of the respiratory hypoxic drive, observable 10 min after infusion commencement and for the duration of the infusions.[48] A bolus dose of naloxone (0.6 μg/kg) was administered after 95 min of the continuous remifentanil infusion. There was no reversal effect of naloxone on the high dose and only a modest effect on the low dose of remifentanil. The two possible explanations of this lack of reversibility of remifentanil by naloxone discussed are (1) even the low-dose infusion maintained a concentration of remifentanil at the receptor level that the (fixed) dose of naloxone was unable to displace or (2) the thermodynamics of the remifentanil—receptor interaction is such that competitive antagonism is difficult to demonstrate.[48] In comparison, for remifentanil with its ultra-short half-life, simply stopping the infusion was a very effective way of reversing the respiratory actions; a reversal complete within approximately 10 min of infusion termination, an effect just as rapid as the naloxone-induced reversal of alfentanil-induced effects. Hence, for remifentanil, reversal of adverse events is preferable by termination of infusion, rather than administration of naloxone. If naloxone is used for reversal, however, higher than standard doses may be required or a continuous infusion needs to be applied.

Notably, in a recent study comparing remifentanil and fentanyl for postoperative pain control after abdominal hysterectomy, the patient group receiving remifentanil infusions (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 2 days) was associated with 3 episodes of serious respiratory depression (3 of 28 patients, 10.7%), and the study was closed.[52] No events of serious respiratory depression were observed in the fentanyl group (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Respiratory depression and apnea, therefore, may be of particular concern with remifentanil infusion. Respiratory complications with remifentanil may further be associated with its rapid onset where the carbon dioxide ventilation response curve (the relationship between minute volume and arterial carbon dioxide concentration) is altered before the patient's arterial carbon dioxide concentration rises sufficiently to sustain ventilatory drive.[17,53,54]

Reversal of the Partial Opioid Receptor Agonist Buprenorphine

A commonly used long-lasting, partial opioid agonist that has a complex interaction with naloxone is buprenorphine. Some early clinical studies indicated that, typical of opioids, buprenorphine could induce respiratory depression, but that this effect was resistant to antagonism by naloxone requiring higher than usual doses for even a partial reversal.[55–57] In a study in human volunteers, neither the level of sedation nor respiratory depression induced by buprenorphine (0.3 mg/70 kg) was consistently reversed by naloxone, even with high doses (10 mg).[58]

Buprenorphine has a half-life in plasma of approximately 3 h, although its duration of action is considerably longer

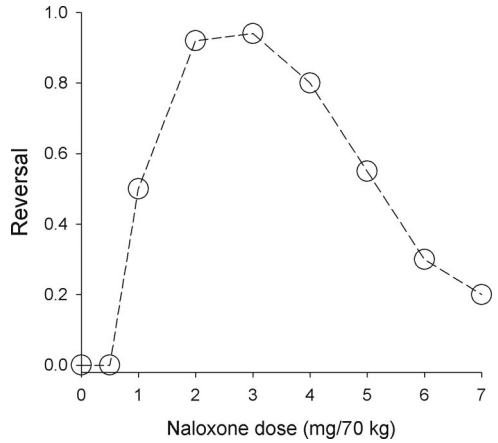

Fig. 4. Bell-shaped naloxone reversal of opioid-induced respiratory depression. Data point are mean values. y-axis: 0 = reversal no better than placebo, 1 = full reversal. Data redrawn, with permission, from van Dorp *et al*.[41]

(>6 h).[59,60] Unlike for the opioids discussed so far in this review, the duration of the biologic actions of buprenorphine is governed primarily not by plasma half-life but by other factors. Gal[58] postulated that the difficulty in reversing buprenorphine-induced respiratory depression by naloxone reflected the slow receptor kinetics of buprenorphine with the μ-opioid receptor. Although buprenorphine has a high affinity for various opioid receptors (it is an agonist at the μ-opioid receptor and the opioid receptor-like 1 receptor and an antagonist at the κ-opioid receptor),[61] its effect at the μ-opioid receptor is most important for respiratory depression. Buprenorphine pharmacology and its complex interactions with naloxone have been fully investigated in human volunteers in a recent series of studies in our laboratories in Leiden.[11,41,45] Although buprenorphine induces significant respiratory depression at clinical doses, respiratory depression exhibits an apparent maximum or ceiling effect typical for a partial agonist at the μ-opioid receptor.[11] However, the potential benefit of a ceiling effect in the side-effect profile of buprenorphine is counteracted to some extent by its resistance to naloxone-induced reversal.[41] In a naloxone dose-response study in human volunteers, reversal of intravenous buprenorphine (0.2 mg) with standard doses of intravenous naloxone (up to 0.8 mg) had no effect. Increasing the dose of naloxone to 2–4 mg did result in full reversal of the buprenorphine-induced effects, although further increasing the naloxone dose (5–7 mg) caused a decline in reversal activity. Therefore, the full dose-response relationship was bell shaped, as shown in figure 4.[41] A bell-shaped dose-response relationship has also been observed for other buprenorphine-induced actions.[61] These data indicated that reversal of buprenorphine-induced respiratory depression is possible but depends on the dose of naloxone and its inverse U-shaped dose-response relationship. With the far more rapid biologic half-life of naloxone, compared with buprenorphine, the respiratory depressant actions of buprenorphine outlast the effects of naloxone-induced reversals from bolus injections, even using higher doses of the reversing agent. A naloxone regimen consisting of a bolus administration (2–3 mg) followed by a continuous infusion (4 mg/h), however, provided full reversal of buprenorphine within 40–60 min, and this reversal was sustained.[41] A pharmacokinetic-pharmacodynamic model of buprenorphine-induced respiratory depression by naloxone has been developed.[45] For buprenorphine, the $t_{½}k_{e0}$ was 75 min in the presence of naloxone, demonstrating a similar value to that derived previously in the absence of naloxone. This slow equilibration is paralleled by slow receptor association/dissociation kinetics ($t_{½}k_{off}$ = 70 min).[45,62] The kinetic values for buprenorphine are in marked contrast to the rapid kinetics displayed by naloxone ($t_{½}k_{off}$ = 0.8 min, $t_{½}k_{e0}$ = 6.5 min).[43,45] Hence, reversal of buprenorphine by naloxone is characterized by the contrasting slow kinetics of receptor site equilibration and receptor dissociation of buprenorphine with the rapid kinetics of naloxone. This pharmacokinetic/pharmacodynamic model accurately predicts the reversal of buprenorphine by naloxone up to doses of 4 mg 70 kg^{-1} h^{-1}, where almost complete reversal is accomplished. Hence, the pharmacokinetic/pharmacodynamic model provides a good theoretical basis for the interactions between buprenorphine and naloxone. The cause for the bell-shaped naloxone-dose response curve in reversing buprenorphine-induced respiratory depression remains unknown. A possible mechanism may be that buprenorphine acts at two opioid receptor subpopulations, one mediating the agonist properties at low dose and the other mediating the antagonistic properties at high dose.[11] Alternatively, antagonism of the action of buprenorphine at other opioid receptors, such as the opioid receptor-like 1 receptor, have been postulated.[63]

Naloxone Side Effects

Early clinical experience in the 1970s suggests that naloxone use may, under certain specific circumstances, cause serious and possibly life-threatening side effects, such as pulmonary edema, cardiac arrhythmias, hypertension, and cardiac arrest.[64–68] All the patients described in these case reports were postoperative patients experiencing (severe) pain and stress. Even in the most recent prospective study in patients who were comatose due to opioid overdose, some serious complication were seen. Of the 453 patients treated with naloxone, 6 (1.3%) suffered complications such as cardiac arrest, pulmonary edema, and epileptic seizures,[69] with the primary cause of cardiorespiratory complications from naloxone being a massive release of catecholamines.[69] When naloxone is given to a patient who is hypovolemic, hypotensive, and/or previously (before opioid treatment) in severe pain or stress, high-dose naloxone and/or rapidly infused naloxone (*i.e.*, not titrated) can cause catecholamine-mediated cardiac arrhythmias and vasoconstriction. The vasoconstriction may lead to a fluid shift from the systemic circulation to the pulmonary vascular bed, resulting in pulmonary edema.[64] When naloxone is titrated to effect, it is generally safe. Stud-

ies in animals and healthy volunteers confirm the safety of naloxone use in patients, even at higher doses up to 10 mg or on constant exposure to intermediate to high concentrations of naloxone during 1 to 2 h.[41,58]

The possibility of cardiovascular complications and renarcotization (with recurrence of sedation and respiratory depression) should always be anticipated when treating a patient with naloxone. Consequently, cardiorespiratory monitoring is a primary requirement for the patient receiving naloxone, especially when the patient has just received an opioid dose through the intravenous route or is "sympathetically" unstable.

Reversal of Respiratory Depression by Nonopioids

For many situations in which respiratory depression is a critical factor in postoperative care, the proper use of naloxone will provide corrective treatment. There is, however, considerable interest and a potential need for improved therapeutic interventions using nonopioid drugs. As discussed earlier, opioid-induced respiratory depression and analgesia are inextricably linked by their mediation through the μ-opioid receptor. Reversal of opioid-induced respiratory depression by naloxone, therefore, may lead inevitably to the loss of analgesia, which creates difficulties to patient care. Furthermore, in case of a mismatch between the pharmacokinetics and pharmacodynamics of the opioid agonist and antagonist, the possibility for renarcotization may be a cause for concern. Therefore, there may be real therapeutic benefits in adding effective nonopioids to the armamentarium of drugs available for use in the treatment of severe respiratory depression. The remainder of this review will consider some advances and possibilities in the development of nonopioids for the treatment and prevention of respiratory depression.

5-Hydroxytryptamine (Serotonin, 5HT) Receptor Ligands

Respiratory drive is controlled by key centers in the brainstem (fig. 5), such as the rhythm-generating pre-Bötzinger complex that receive modulating inputs from the cortex and from central and peripheral chemoreceptors. The inhibition of this dynamic respiratory control system by opioids has been reviewed recently.[70] Respiratory drive may be restored by manipulation of neuronal transmitter systems in those regions, particularly serotinergic systems. 5HT enhances activity in respiratory neurons primarily through actions at 5-HT_{1A} (sometimes referred to as $5HT_{1A/7}$ or $5HT_{1like}$), $5HT_7$, and $5HT_{4a}$ receptors.[71] 5HT-based approaches, unlike opioid antagonists, do not usually demonstrate any antagonism of opioid-induced analgesia.

$5HT_{1A}$ and $5HT_7$ Receptor Agonists. Perhaps, key to consideration of the development of new 5HT receptor ligands in respiratory depression is their actions at the pre-Bötzinger complex, an area of the ventrolateral medulla (identified in animals but not to date in humans) that generates respiratory

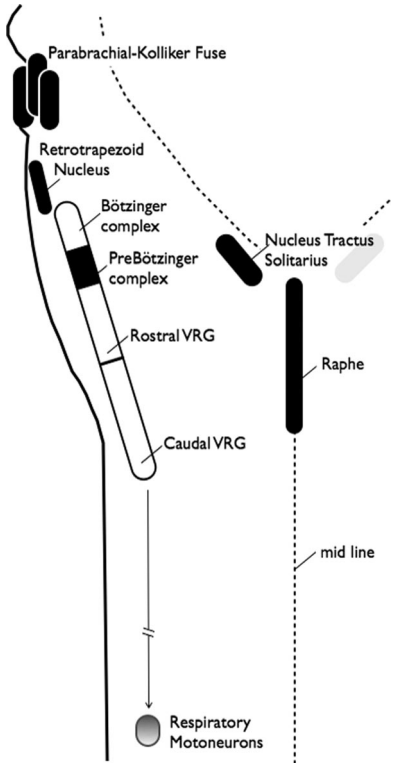

Fig. 5. Simplified schematic representation of the ventral aspect of the (rat) brainstem. The retrotrapezoid nucleus and midline raphe nuclei contain brainstem carbon dioxide–sensitive neurons (central chemoreceptors) that activate premotor neurons of the ventral respiratory group (VRG) that includes the pre-Bötzinger complex, an area with respiratory rhythm-generating neurons. Afferent sensory input from the peripheral chemoreceptors of the carotid bodies activates the nucleus tractus solitarius, which also projects to the VRG. The VRG send signals to respiratory motoneurons in the spinal cord and phrenic nucleus that control intercostal muscles and the diaphragm. Another structure containing respiratory neurons is the pontine respiratory group (parabrachialis medialis and Kolliker-Fuse nucleus) that is implicated in volume control. Other areas involved in ventilatory control (such as the locus coeruleus and areas in the cerebellum) are not depicted.

rhythm.[72–74] Although there are mixed reports in the literature of the effects of $5HT_{1A}$ agonists on respiratory function, more recent studies in a variety of animal species *in vivo* and *in vitro* seem to show that administration of $5HT_{1A}$ agonists, such as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) or the partial agonist buspirone, reverse opioid-induced respiratory depression without affecting antinociception.[75–79] It is thought that enhancement of synaptic inhibition within the pre-Bötzinger complex may be a key site of action of 8-OH-DPAT and buspirone.[80–83] However, respiratory centers in the brainstem also receive modulatory input from other brain areas, which may also be affected by opioids and $5HT_{1A}$ agonists. Medullary raphe neurons, for example, may also be important in determining the overall effects on respiratory depression.[70,84–86] Medullary raphe neurons project to respiratory centers, and activation of $5HT_{1A}$ receptors on raphe neurons may contribute significantly to respiratory restoration by modulating central

expiratory neurons and spinal motorneurons.[84–86] $5HT_{1A}$ receptor influence affects many of the complex constituent mechanisms that together determine respiratory outcome and its manifold expressions such as breathing rate, tidal volume, hypoxic ventilatory response, *etc*., including an influence on related and interacting components such as the cardiovascular system.[77]

One difficulty in interpreting the effects of 5HT ligands in terms of actions at individual 5HT receptors is frequently that many of the ligands available do not demonstrate a high enough degree of selectivity to enable a clear derivation of the effect of that ligand among the overall plethora of 5HT receptors (13 5HT receptors are acknowledged in the recent receptor classification review).[87] Such is the case with 8-OH-DPAT, which has a high affinity for both $5HT_{1A}$ and $5HT_7$ receptors. Because buspirone is not an agonist at $5HT_7$ receptors but has similar actions to 8-OH-DPAT on respiratory systems, there is a tendency to equate the actions of 8-OH-DPAT with $5HT_{1A}$ receptors. However, the potential of the importance of $5HT_7$ receptors in the pre-Bötzinger complex and in the pulmonary vasculature should not be overlooked and ligands with greater selectivity are clearly required to resolve the contributions of $5HT_{1A}$ and $5HT_7$ receptors.[70,76] A further restriction of the available $5HT_{1A/7}$ receptor ligands is that an even fewer number of compounds are licensed for study in humans. Buspirone may be used clinically, and there are anecdotal clinical reports of buspirone improving respiratory dysfunction, for example, postoperatively after removal of an astrocytoma, in Rett syndrome and after a brainstem infarction.[88–91] However, in a double-blinded, placebo-controlled crossover study in 12 healthy volunteers, buspirone (60 mg orally) failed to demonstrate reversal of morphine-induced respiratory depression (30 mg/70 kg intravenously).[91] From our earlier discussions with regard to the use of opioid antagonists for reversal of respiratory depression, any study of this kind must take into consideration both pharmacokinetic and pharmacodynamic considerations. This is discussed by the authors of the buspirone study in healthy volunteers who, using nonparametric pharmacokinetic/pharmacodynamic modeling with the available data on buspirone, concluded that, in this study, the effect-site concentrations of buspirone achieved in the brain were lower than those estimated in studies with rats.[88] The inability of buspirone to reverse morphine-induced respiratory depression, therefore, may be due to inadequate buspirone dosing. However, higher doses of buspirone were contraindicated because, in the healthy volunteers, buspirone (60 mg) significantly increased morphine-induced nausea.[91] Therefore, buspirone would not seem to be an adequate clinical tool to treat opioid-induced respiratory depression or to explore $5HT_{1A}$ mechanisms in man.

$5HT_{4a}$ Receptor Agonists. $5HT_{4a}$ receptors are also expressed on neurons of the pre-Bötzinger complex and are coexpressed with opioid μ-receptors.[92–94] $5HT_{4a}$ agonists do not influence opioid-induced analgesia because $5HT_{4a}$ receptors are absent from pain-processing regions.[94] Stimulation of $5HT_{4a}$ receptors in the pre-Bötzinger complex in rats by the agonist BIMU8 has been shown to protect spontaneous respiratory activity and to reduce or abolish fentanyl-induced respiratory depression.[92] In another species, the goat, an alternative $5HT_{4a}$ agonist, zacopride, reversed etorphine-induced respiratory depression without affecting immobilization or sedation.[76] The functional antagonism of opioids and $5HT_{4a}$ agonists on rhythms in the pre-Bötzinger complex are thought to be due to convergence of neuronal signaling due to their opposite effects on cyclic adenosine monophosphate; stimulation of μ-opioid receptors resulted in a decrease in cyclic adenosine monophosphate and decreased inspiratory drive, whereas stimulation of $5HT_{4a}$ receptors induced an increase in cyclic adenosine monophosphate and increase in inspiratory drive.[92,94]

To investigate the potential clinical benefits of $5HT_{4a}$ agonists in man, the $5HT_{4a}$ agonist mosapride has been investigated in a double-blinded, crossover study in healthy volunteers.[95] Twelve healthy volunteers received oral doses of mosapride (5 mg daily for 5 days), and on the day of testing, three doses of mosapride (5 mg) were administered at 90-min intervals, the second dose was administered concomitantly with morphine (15 mg/70 kg), with a similar dose of morphine being further administered within 2 h. Mosapride had no effect on the respiratory depression induced by morphine. As with the similar clinical study with buspirone in healthy volunteers,[91] a pharmacokinetic/pharmacodynamic model showed that the negative results with mosparide may be attributable to the low potency and/or limited central effect-site concentrations of mosapride being achieved in the clinical study compared with the study in the rat.[95] However, both the buspirone and mosapride studies show the value of pharmacokinetic/pharmacodynamic modeling in the interpretation of early clinical data, and neither study should prevent future clinical possibilities of $5HT_{1A/7}$ or $5HT_4$ receptor agonists from being considered.

Ampakines

In recent years, there has been considerable development in our understanding of the role of the excitatory glutamatergic transmitter system and of glutaminergic dysfunction in the central nervous system. Much of that focus has been directed toward pharmacological blockade of the *N*-methyl-D-aspartate receptor, but for many clinical impairments, metabotropic glutamate receptors and particularly modulators of the α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA, fig. 6) receptors seem to offer interesting prospects.[96] AMPA receptor modulators do not bind directly to the glutamate binding site but to an allosteric pocket within the receptor complex that allows the modulator to augment the function of the activated AMPA receptor but has no intrinsic activity itself at the receptor. At first sight, one essential difficulty of this approach to drug development may be the ubiquitous nature of glutaminergic transmission within the central nervous system, leading to a general enhancement of excitatory activity with little opportunity to

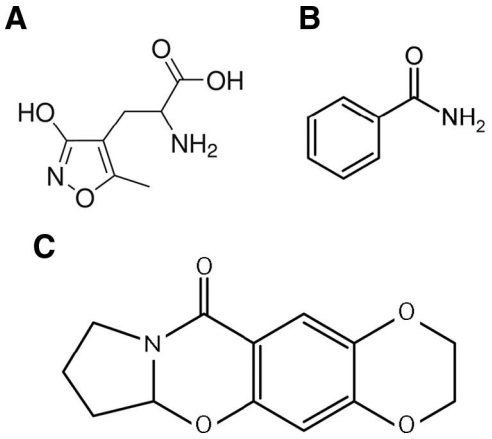

Fig. 6. Chemical structures of (*A*) α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA), (*B*) benzamide, and (*C*) CX614.

achieve drug-induced selective actions. However, it seems that AMPA receptor structure is not uniform across the brain, and AMPA modulation may operate within specific malfunctioning areas without leading to generalized behavioral activity or widespread excitotoxicity, thereby enabling improvement in specific disorders of impaired neuronal glutaminergic function, such as cognitive disorders, attention deficit hyperactivity disorder, and schizophrenia.[97,98] This may extend to actions to improve respiratory depression. Within the pre-Bötzinger complex, AMPA receptors are important for maintaining rhythmicity,[99,100] and hence, blockade of AMPA sites results in an inhibition of respiration and their enhancement leads to increases in respiratory frequency.[99]

Several distinct classes of positive AMPA receptor modulators have been described including aniracitam, benzothiadiazides, and related 7-chloro-3-methyl-3–4-dihydro-2H-1,2,4 benzothiadiazine S,S,-dioxide and 2,6,7-trioxa-1-phosphabicyclo[2.2.2.]octane-4-methanol-1-oxide compounds, biarypropylsulfonides (LY392098 and others), but the most interesting to date seem to be a group of benzamides (fig. 6), collectively called ampakines, examples of which are CX516, CX546, CX614, and CX717.[96,101] The AMPA receptor is composed of arrangements of receptor subunits, and different ampakines may show subunit preferences allowing differentiation of their modulatory actions; positive enhancement of AMPA receptors by CX516 is by increase in the amplitude of synaptic responses, while that of CX546 is by prolongation of the duration of synaptic action and CX516 accelerates channel opening, whereas CX546 primarily slows channel closing.[102] CX546 binds to the AMPA receptor complex at an allosteric site within the AMPA receptor complex in its agonist bound state, not to its desensitized or agonist-free state, and modulates the kinetics of deactivation and desensitization.[102–104] CX614 is closely related to CX546 but is more sterically hindered and has been used to further define the allosteric binding site and actions of the ampakines.[105] Actions within the pre-Bötzinger complex, probably underlie the observed actions of CX546 and CX717 to reverse the opioid-induced inhibition of respiratory drive in medullary slice and brainstem-spinal cord preparations *in vitro* and plethysmography *in vivo* in the rat, without antagonizing fentanyl-induced antinociception (fig. 7).[106,107] Hence, in the rat, the ampakines CX546 and CX717 act as a powerful stimulant of respiratory frequency and tidal volume after respiratory depression induced by opioid μ-receptor agonists.

To date, most testing on ampakines has been done in animals. A placebo-controlled pilot study of the related ampakine CX516 combined with clozapine in schizophrenia demonstrated the drug to be well tolerated and was associated with improvements in attention and memory.[108] In a preliminary report, German researchers showed improvement of respiratory rate by the oral administration of a single dose (1500 mg) CX717 but not hypercapnic minute venti-

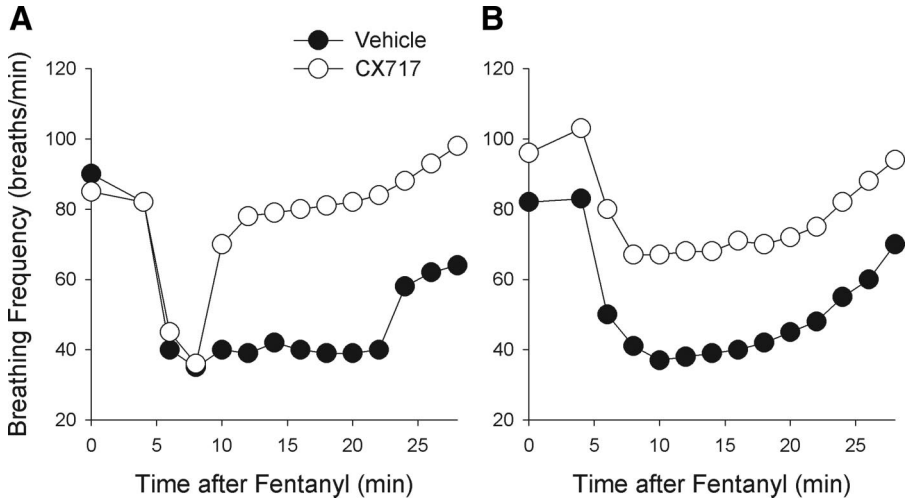

Fig. 7. Effect of the ampakine CX717 on fentanyl-induced respiratory depression in the adult rat. (*A*) A measure of 60 μg/kg intravenous fentanyl followed by 15 mg/kg intravenous CX717 approximately 6 min after the fentanyl infusion. (*B*) Pretreatment with CX717 (15 mg/kg intravenous) followed by 60 μg/kg intravenous fentanyl. Data are population means with 9 to 10 animals per group. Data redrawn, with permission, from Ren *et al.*[107]

lation during low-dose alfentanil infusion without affecting antinociception.‡

Minocycline, a Microglial Inhibitor

A further action of the ampakine CX546 is the enhancement of astrocyte metabolism, which increases glucose use and lactate production and may play some role in cognition enhancement.[109] With regard to respiratory depression, however, the action of opioids on immune cells such as astrocytes and microglia may represent a further novel target for drug development. Opioid activation of the immune system may act as a homeostatic mechanism to switch off analgesia mediated within the central nervous system by the release of endogenous opioids to nociceptive stimuli.[110] Conversely, inhibitors of glial activation have been shown to enhance the analgesic efficacy of acute and chronic morphine.[111] A recent study has investigated whether minocycline, a tetracycline-derivative and an inhibitor of microglial activation,[112] may also influence opioid-induced respiratory depression as well as analgesia in rats.[113] In agreement with general expectations, minocycline enhanced antinociception induced by morphine (this effect is independent of its antimicrobial properties). Furthermore, using full body plethysmography and pulse oximetry, minocycline was shown to attenuate the respiratory depressant effects of morphine on measures such as tidal volume, minute volume, inspiratory and expiratory forces, and blood oxygen saturation, although minocycline did not affect respiratory rate.[113] Unusually, therefore, the same doses of minocycline demonstrated opposing effects on opioid-induced analgesia and respiratory depression in the rat, enhancing the former while suppressing the latter. The apparent inhibition of tidal volume and other measures, but not respiratory rate, is speculated to arise from glial activation mechanisms in brain areas that are involved primarily in control of tidal volume, such as neurons of the pontine respiratory group (nucleus parabrachialis medialis and Kolliker-Fuse nucleus), but not in areas involved in respiratory frequency, such as the pre-Bötzinger complex.[113] Hence, minocycline suggests an interesting possibility for the development of inhibitors of glial activation for reversal or prevention of opioid-induced respiratory depression that may simultaneously enhance opioid-induced analgesia and offer a site of action different from that hypothesized for the 5HT receptor agonists or ampakines.

Conclusion

There is ample evidence that opioid analgesics interact with ventilatory control, causing some degree of respiratory depression.[7,8,114,115] However, opioid treatment of moderate to severe pain is generally safe with about 0.5% or less events related to respiratory depression. However, there are still fatal outcomes of opioid analgesic use even under controlled conditions in the clinical settings often related to opioid overdose-related respiratory depression.[115] The only treatment currently available to reverse opioid respiratory depression is by direct antagonism of the site of action of opioid effect, the μ-opioid receptor, using intravenous naloxone. Naloxone use is effective although its efficacy depends on many factors and includes the pharmacokinetics and pharmacodynamics (including receptor kinetics) of the opioid analgesic, which requires antagonism. Because of the relative short elimination half-life of naloxone, the clinical approach to severe opioid-induced respiratory depression would be to titrate naloxone to effect and subsequently continue treatment by continuous infusion until chances for renarcotization have diminished. New treatments and/or approaches to prevent opioid respiratory depression without affecting analgesia have led to the experimental application of new agents such as serotinine agonists, ampakines, and the antibiotic minocycline. Lacking so far are controlled human trials showing efficacy to treat high-dose opioid toxicity. There are other promising agents available that deserve study, for example, inhibitors of the sodium/proton exchanger type 3 (NHE3) that have a stimulatory effect on breathing due to an action within central respiratory pathways.[116,117]

‡ Available at: http://www.medicalnewstoday.com/articles/124558.php. Accessed June 18, 2009.

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